Efficacy and safety of larotrectinib in TRK fusion-positive primary central nervous system tumors

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Conflicts of Interest

SGD has received fees for consulting and advisory board roles from Bayer and Loxo Oncology and has received travel expenses from Loxo Oncology, Roche/Genentech, and Salarius Pharmaceuticals.

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S.G-M has received fees for advisory boards and travel expenses from Loxo and Bayer

JCC has received fees for advisory board and educational roles from Bayer

KN has received fees for advisory board roles and consulting from Bayer, Y-mAbs Therapeutics and EUSA Pharma.

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Authorship

Conception and study design: TL, AD, DH, FD, SP, EDL, LD, RN

Data acquisition, analysis, and interpretation: all authors

Writing and review: all authors

Abstract

Background: Larotrectinib is a first-in-class, highly selective tropomyosin receptor kinase (TRK) inhibitor approved to treat adult and pediatric patients with TRK fusion-positive cancer. The aim of this study was to evaluate the efficacy and safety of larotrectinib in patients with TRK fusion-positive primary central nervous system (CNS) tumors.

Methods: Patients with TRK fusion-positive primary CNS tumors from two clinical trials (NCT02637687, NCT02576431) were identified. The primary endpoint was investigator-assessed objective response rate (ORR).

Results: As of July 2020, 33 patients with TRK fusion-positive CNS tumors were identified (median age: 8.9 years; range: 1.3–79.0). The most common histologies were high-grade glioma (HGG; *n* = 19) and low-grade glioma (LGG; *n* = 8). ORR was 30% (95% confidence interval [CI]: 16–49) for all patients. In all patients, the 24-week disease control rate was 73% (95% CI: 54–87). Twenty-three of 28 patients (82%) with measurable disease had tumor shrinkage. The 12-month rates for duration of response, progression-free survival, and overall survival were 75% (95% CI: 45–100), 56% (95% CI: 38–74), and 85% (95% CI: 71–99), respectively. Median time to response was 1.9 months (range 1.0–3.8 months). Duration of treatment ranged from 1.2–31.3+ months. Treatment-related adverse events were reported for 20 patients, with Grade 3–4 in 3 patients. No new safety signals were identified.

Conclusions: In patients with TRK fusion-positive CNS tumors, larotrectinib demonstrated rapid and durable responses, high disease control rate, and a favorable safety profile.

Key words: Larotrectinib, *NTRK* gene fusions, TRK fusion, primary CNS tumors

Key points:

- Larotrectinib demonstrated rapid and durable responses in TRK fusion primary CNS tumors
- Responses were seen in patients with low- and high-grade gliomas as well as non-gliomas
- This analysis is the largest report to date of a TRK inhibitor studied in primary CNS cancers

Importance of the Study

There is a high unmet need for tolerable targeted therapeutic options for patients with tropomyosin receptor kinase (TRK) fusion-positive primary central nervous system (CNS) tumors, particularly for pediatric patients for whom radiotherapy may have significant negative long-term consequences on neurocognitive functions. Larotrectinib is a first-in-class, highly selective TRK inhibitor approved to treat adult and pediatric patients with TRK fusion-positive cancer. In patients with TRK fusion-positive CNS tumors, larotrectinib demonstrated rapid and durable responses with a high disease control rate and favorable safety profile in various tumor types including low- and high-grade gliomas as well as non-gliomas. All complete and partial responses in this analysis occurred in pediatric patients, suggesting that larotrectinib may be a valuable therapeutic option for delaying or avoiding the need for radiotherapy in this population. This is the largest report to date of a TRK inhibitor studied in primary CNS cancers.

Introduction

The tropomyosin receptor kinase (TRK) family of receptors is composed of TRKA, TRKB, and TRKC, which are neurotrophic tyrosine receptor kinase (*NTRK*) proteins encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively.[1,2] TRK receptors are predominantly expressed in neuronal tissue and play an essential role in the normal development and function of the nervous system.[1,3,4] Activation of TRK receptors by their respective ligands (neurotrophins) affects various neuronal events during embryogenesis and beyond, including neuronal cell differentiation, survival and proliferation, synaptic formation and plasticity, membrane trafficking, and axon and dendrite formation.[3-5] TRK receptors play important roles in nociception, proprioception, memory formation and retention,[4] pain and temperature sensation,[6,7] appetite control, and learning.[8-10]

NTRK gene fusions occur when the 3' region of the *NTRK* gene encoding the tyrosine kinase domain is joined in-frame with the 5' end of a fusion partner gene, either by intra- or interchromosomal rearrangement.[5] The resulting fusion oncogene leads to the expression of a chimeric protein that retains the tyrosine kinase domain, is constitutively active, and drives downstream signaling.[5]

NTRK gene fusions have been identified in a variety of adult and pediatric tumors and are estimated to occur in up to 1% of all solid tumors.[2,11,12] Importantly, *NTRK* gene fusions are found in primary central nervous system (CNS) tumors, particularly in children. *NTRK* gene fusions occur in up to 2% of adult primary brain tumors (e.g. gliomas of all grades),[13-15] while in the pediatric population *NTRK* gene fusions have been observed in up to 5.3% of high-grade gliomas and 2.5% of low-grade gliomas.[14] Of note, in children, high-grade gliomas harboring *NTRK* gene fusions appear to be enriched in patients with non-brainstem tumors and in those <3 years old.[16-18]

Larotrectinib is a first-in-class, highly selective small-molecule inhibitor of TRKA, TRKB, and TRKC. It was first approved by the US Food and Drug Administration in November 2018 for the treatment of adult and pediatric patients with solid tumors harboring an *NTRK* gene fusion without a known acquired resistance mutation which are metastatic or where surgical resection is likely to result in severe morbidity and who have no satisfactory

alternative treatments or have progressed following treatment.[19] As of October 2021, larotrectinib was subsequently approved for use in more than 40 countries, notably being the first tumor agnostic therapy to be approved by the European Medicines Agency.[20] A combined analysis of 159 patients with solid non-CNS tumors from three adult/pediatric phase I/II trials of larotrectinib (NCT02122913, NCT02637687, NCT02576431) showed a durable objective response rate (ORR) by investigator assessment of 79%, regardless of age or tumor type. At the data cut-off date of February 2019, 69% were still receiving treatment or had undergone surgery with curative intent. Adverse events (AEs) related to larotrectinib were predominantly grade 1 or 2.[21]

In prior reports, larotrectinib has been shown to have antitumor activity against TRK fusion-positive primary solid tumors that have metastasized to the CNS.[21,22] In a post-hoc exploratory analysis of the integrated dataset of 159 patients, 12 evaluable patients with brain metastases achieved an ORR of 75% across all sites of disease. The 3 patients with measurable intracranial disease at baseline had intracranial tumor reductions of 14%, 46%, and 100%, demonstrating the brain penetrance of larotrectinib.[21] One prior case report demonstrated activity of larotrectinib in a child with a high-grade glioma harboring an *NTRK* gene fusion,[23] but there is otherwise a paucity of data on the role of larotrectinib in primary CNS tumors. Here we present the efficacy and safety of larotrectinib in a cohort of adult and pediatric patients with TRK fusion-positive primary CNS cancer.

Materials and Methods

All patients with primary CNS tumors harboring an *NTRK* gene fusion detected by local/regional molecular testing and treated with larotrectinib in two clinical trials (NCT02637687 [SCOUT; phase I/II] and NCT02576431 [NAVIGATE; phase II]) as of July 20, 2020 were identified and included in the current analysis. Both trials included pediatric patients: SCOUT enrolled patients from 0–21 years of age and NAVIGATE enrolled patients ≥12 years of age. Eligibility criteria for both trials allowed patients with primary CNS tumors, regardless of histology and grade, who had progressed or were non-responsive to available therapies, were unfit for standard chemotherapy, or for whom no standard or curative therapy was available. Patients with neurologically unstable or rapidly progressive primary CNS tumors were not eligible. Patients who had previously experienced progression while receiving approved or investigational TRK inhibitors were also excluded. Patients who had received a TRK inhibitor for <28 days of treatment and discontinued because of intolerance remained eligible. Larotrectinib was administered at the recommended dose of 100 mg (adult patients) or 100 mg/m^2 (pediatric patients; maximum of 100 mg) twice daily and continued until disease progression, withdrawal, unacceptable toxicity, or loss of clinical benefit. Patients could continue larotrectinib post-progression if, in the opinion of the investigator, they continued to derive clinical benefit.

The main efficacy endpoint of these trials was ORR. Intracranial response to treatment was an endpoint for the current analysis and was investigator assessed using Response Assessment in Neuro-Oncology (RANO) criteria based upon serial magnetic resonance imaging or computerized tomography scans.[24] For this analysis, Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[25] per investigator assessment was used for target lesions that were not measurable with RANO at baseline or for tumor types for which RANO measurement is difficult (e.g. pediatric high- and low-grade gliomas, leptomeningeal tumors).[26-31] Secondary endpoints included duration of response, progression-free survival, and overall survival. The 24-week disease control rate, defined as the proportion of patients with best overall response of confirmed complete response, partial response, or stable disease lasting 24 weeks or more (measured from the date of the first dose of larotrectinib) following the initiation of larotrectinib, was calculated for the overall cohort as well as separately for adult and pediatric patients. The main safety endpoint of these trials was toxicity as assessed by Common Terminology Criteria for Adverse Events, version 4.03.[32]

All studies were done in accordance with the standard of good clinical practice, the principles expressed in the Declaration of Helsinki, and all applicable country and local regulations. Protocols were approved by an institutional review board or independent ethics committee at each investigative site. All patients (or parents or guardians of minor patients) provided written informed consent before the initiation of any study-related procedures.

Results

Patient characteristics

A total of 33 patients with primary CNS tumors harboring an *NTRK* gene fusion were enrolled (**Table 1**). Seventeen patients (52%) were male. The median age at enrollment was 8.9 years (range 1.3–79.0 years); 26 patients (79%) were children (<18 years). Patients were heavily pre-treated, with 15 patients (45%) having 2 or more prior lines of therapy; 28 patients (85%) had received prior systemic therapy. Best response to last systemic treatment was complete response in 2 patients (6%), partial response in 1 patient (3%), stable disease in 11 patients (33%), and progressive disease in 8 patients (24%), and unknown or unevaluable in the remaining 11 patients (33%). Prior to enrollment, 22 patients (67%) had undergone surgery and 18 patients (55%) had received radiotherapy.

The patients had tumors harboring gene fusions involving *NTRK2* (*n* = 24), *NTRK1* (*n* = 5), and *NTRK3* (*n* = 4). Patient-level details, including methylation profiling and concurrent molecular alterations for a subset of patients with available data, are shown in **Supplementary Table 1**.

Efficacy

At the time of data cut-off, all 33 patients were evaluable for ORR. Twenty-eight patients had measurable disease at baseline, with tumor response in 23 patients assessed by the investigator based on RANO sum of products of diameters. The other 5 patients with measurable disease at baseline were assessed with RECIST v1.1 as their target lesions were inadequate or difficult for RANO assessment. The remaining 5 evaluable patients had baseline target lesions that were not measurable by either RANO or RECIST v1.1 so were excluded from assessment of change in target lesion size (**Figure 1A**). The ORR for all 33 evaluable patients was 30% (95% confidence interval [CI]: 16–49; *n* = 10), with responses seen in high- and low-grade tumors, across tumor entities, and regardless of the type of *NTRK* gene fusion involved (**Table 2**). In the 26 pediatric patients, the ORR was 38% (95% CI: 20–59). The ORRs for the 13 pediatric high-grade gliomas and 7 pediatric low-grade gliomas were 38% (95% CI: 14–68) and 43% (95% CI: 10–82), respectively. Best overall response for all patients was complete response in 3 patients (9%; 2 in pediatric high-grade gliomas and 1 in pediatric non-glioma; see **Figure 2** for case study), partial response in 7 patients (21%; 3 in pediatric high-grade gliomas with 2 pending confirmation, 3 in pediatric low-grade gliomas, and 1 in pediatric non-glioma), stable disease in 20 patients (61%), and progressive disease in 3 patients (9%; all high-grade gliomas). The 24-week disease control rate for all patients was 73% (95% CI: 54–87). For the pediatric cohort, the 24-week disease control rate was 77% (95% CI: 56–91; 69% [95% CI: 39–91] for pediatric high-grade gliomas and 100% [95% CI: 59–100] for pediatric low-grade gliomas). For the adult cohort, the 24-week disease control rate was 57% (95% CI: 18–90; 50% [95% CI: 12–88] for adult high-grade gliomas and 100% [95% CI: 3–100] for adult low-grade gliomas). Of the 28 patients who had measurable disease, 23 (82%) achieved tumor shrinkage (**Figure 1A**).

The median time to response was 1.9 months (range 1.0–3.8 months). Median duration of response was not reached (range 3.8–22.0+ months) at a median follow-up of 12.0 months. At the time of data cut-off, 18 patients (55%) remained on treatment (**Figure 1B**). Fifteen patients (45%; 6 adults and 9 pediatric patients) experienced progression of disease while on treatment; 4 of these patients continued treatment post-progression because clinical benefit was ongoing in the opinion of the investigator, with 2 patients receiving treatment post-progression for >1 month. Median progression-free survival was 18.3 months (95% CI: 6.7–not estimable [NE]) at a median follow-up of 16.5 months, with a 12-month progression-free survival rate of 56% (95% CI: 38–74) and a 24-month progression-free survival rate of 42% (95% CI: 18–65). Median overall survival was not reached (95% CI: 16.9–NE) at a median follow-up of 16.5 months, with a 12-month overall survival rate of 85% (95% CI: 71–99) and a 24-month overall survival rate of 58% (95% CI: 28–88). The duration of treatment ranged from 1.2–31.3+ months (median 11.1 months). At the time of data cut-off, 15 patients (45%) had discontinued treatment, with 14 discontinuing due to progression of disease.

Safety

Of the 33 patients, 31 patients (94%) experienced treatment-emergent AEs, with 13 (39%) experiencing a grade 3 or 4 AE (**Table 3**). 20 patients (61%) experienced an AE deemed by the investigator as related to larotrectinib; 3 of these patients had a grade 3 or 4 AE deemed related to larotrectinib (one event each of gamma-glutamyltransferase increase, hyperglycemia, hypernatremia, hyponatremia, and neutrophil count decrease). Treatment-related neurological AEs were infrequent and mild (grade 1 or 2) and included memory impairment in 2 patients and 1 patient each with headache, dizziness, hallucination, and irritability. Fourteen patients (42%) required dose modifications because of AEs. None of the patients discontinued treatment due to treatment-related AEs. No new safety signals were identified.

Discussion

Despite therapeutic advances, progress in the treatment of primary CNS tumors in particular has been relatively slow due to a number of reasons, including molecular heterogeneity, poor blood-brain barrier penetration of therapeutic agents, and the lack of effective anticancer agents.[26] The results from this analysis demonstrate the activity of larotrectinib in TRK fusion-positive primary CNS tumors regardless of histology, thus confirming its capacity for blood-brain barrier penetrance as previously shown by the response seen in metastases of extracranial tumors to the CNS.[21,22] Therapies used in the current standard of care for primary CNS tumors have limitations that highlight the unmet need for targeted therapies. For example, many chemotherapeutic agents have limited efficacy intracranially and/or demonstrate significant toxicity. In addition, cranial radiotherapy may have significant negative long-term consequences on neurocognitive functions, particularly in children.[33,34] Specifically, pediatric high-grade gliomas are associated with very low survival rates or limited tolerable therapeutic options.[34,35] Therefore, targeted therapy would be especially impactful in these patients by improving disease control and allowing for the delay of other treatments with less favorable risk/benefit profiles.[35,36] As all of the complete responses and partial responses in this analysis occurred in pediatric patients, larotrectinib may be a valuable therapeutic option for delaying or avoiding the need for radiotherapy or as an adjuvant to surgery to preserve neurological function and avoid invasive or potentially debilitating complete tumor resection in this population.[29] The current analysis is the largest report to date of a TRK inhibitor studied in primary CNS cancers. With this study, we further show that clinical trials of adult and pediatric patients with both primary CNS and non-CNS tumors are feasible, which is important when studying rare primary CNS tumors, such as those harboring an *NTRK* gene fusion.

In this cohort of patients with various types of primary CNS tumors harboring an *NTRK* gene fusion, larotrectinib demonstrated marked, rapid, and durable responses, with no new larotrectinib-related safety signals seen. Of these patients, 73% had disease control lasting for at least 24 weeks. The 3 complete responses and 7 partial responses observed all occurred in pediatric patients of varying tumor types and grades (high-grade gliomas, low-grade gliomas, and non-gliomas). However, at present it is difficult to draw conclusions on the apparent differences in efficacy observed between adult and pediatric patients given the small number of patients included in this analysis, particularly for adults. Pediatric gliomas differ from adult gliomas in molecular factors such as biological drivers, DNA copy number, and underlying genetic alterations.[17,18,37,38] Moreover, the frequency of pathologically significant concomitant mutations in TRK fusion-positive gliomas, such as alterations in *IDH*, *H3.3*, and *TP53*, appears to increase with age.[39] While these are potential confounding factors that may

lead to differences in response to larotrectinib between adult and pediatric patients, further investigation in an expanded population is needed to determine if they have any effect on efficacy.

In patients with primary CNS tumors, accurate diagnosis is important as histologic and molecular subtypes are key considerations in treatment, providing additional prognostic information. Molecular biomarkers are increasingly driving diagnostic and treatment decisions, thus molecular profiling of tumors is essential for optimizing treatment and clinical outcomes.[35,40] Indeed, the 2021 World Health Organization Classification of Tumors of the CNS illustrates this paradigm shift as specific molecular markers have become mandatory for the correct diagnosis of several tumor types,[40] although this classification does not currently consider *NTRK* gene fusions. DNA methylation profiling has allowed for subclassification of different CNS tumors that were previously considered homogeneous diseases, reducing the substantial inter-observer variability seen in CNS tumor diagnoses that previously relied on histopathology alone.[41] Notably, methylation profiling studies of gliomas harboring an *NTRK* gene fusion did not report a match between histology and methylation class family.[39] In this current analysis, there was an insufficient number of patients with methylation profiling data available to conclude whether the methylation class families matched with the histologies observed.

Gene fusion events appear to arise more commonly in the *NTRK1* and *NTRK3* genes than in *NTRK2* in most solid tumors, with the exception of brain tumors.[5,11,12,42] This was reflected in this cohort of primary CNS patients, where *NTRK2* gene fusions were the most common type observed. Of note, *BCR* (n = 3), *NACC2* (n = 2), *SPECC1L* (n = 2), *AGAP1* (n = 2), and *GKAP1* (n = 2) were recurrent *NTRK2* fusion partners identified in this cohort. It is still unknown if the specific fusion partner affects the response to larotrectinib, and future

studies may determine whether an association exists. The intracranial efficacy of larotrectinib has been demonstrated in TRK fusion-positive tumors that have metastasized to the brain, and this therapy is usually associated with low toxicity and few high-grade AEs.[21,22,43]

In a pooled safety population of three adult/pediatric phase I/II trials, larotrectinib was well tolerated in patients with non-primary CNS tumors, with treatment-emergent AEs being primarily grade 1 or 2.[21] In the current analysis of patients with primary CNS tumors, the AE profile was consistent with that seen in patients with non-primary CNS tumors. Specifically, treatment-related neurological AEs were infrequent and generally mild in severity as was also observed in patients with non-primary CNS tumors. Given the role that TRK proteins play in the function of the CNS (e.g. proprioception, pain sensation, and memory[4,6,7]), the neurologic on-target AEs observed in both patients with primary CNS and non-primary CNS tumors are not unexpected.[2,11] Data on neurologic effects of long-term treatment with larotrectinib are needed, particularly in the pediatric population due to the biological role of TRK proteins in the development and maintenance of the CNS. In this study with relatively short-term follow-up, larotrectinib appears to be well tolerated.

There were several limitations of the study. Histologic review was performed locally without central review. As the larotrectinib development program enrolled patients across a variety of primary CNS and extra-cranial solid tumor types, with the aim of demonstrating the tumor-agnostic efficacy and safety of larotrectinib, there was less emphasis on the tumor-specific histology details. Detailed methylation data were limited, as complete molecular profiling was not required beyond testing for *NTRK* gene fusions. Similarly, per study protocols, radiological assessments for patients with primary CNS disease were investigator-assessed and collated locally at each study site rather than centrally reviewed. While RANO criteria was used for the majority of patients, RECIST v1.1 was used to assess tumor

response in 5 patients who had target lesions that were not measurable with RANO criteria, including 3 pediatric patients. Pediatric gliomas have clinical and biological features distinct from adult gliomas that make measurement difficult with RANO criteria, which were developed for adults and do not take these differences into consideration.[29-31] Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria have recently been developed to address these challenges; as such, RAPNO criteria can provide a more accurate assessment of pediatric gliomas as compared to RANO.[29,30] However, since the studies were initiated in 2015 prior to the development of the RAPNO criteria, it was not feasible to use RAPNO criteria for this current analysis.

Conclusion

Larotrectinib is active in patients with TRK fusion-positive primary CNS tumors, a population with a high unmet need for effective and tolerable targeted therapeutic options. Confirmed responses and durable disease control were observed in patients with low- and high-grade gliomas as well as those with non-gliomas, with no treatment-related safety concerns. These results further support expanded testing for actionable therapeutic targets, including *NTRK* gene fusions, in patients with primary adult and pediatric CNS tumors.

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Figure legends

Fig. 1 (A) Maximum change in target lesion size for 28 patients with baseline measurable disease[a], and (B) Duration of treatment and response for all patients (*n* = 33)

[a]Tumor responses in patients recorded at data cut-off, based on RANO sum of products of diameters, unless noted otherwise. RECIST v1.1 was used for target lesions that were not measurable with RANO at baseline or for tumor types for which RANO measurement is difficult. Five patients were excluded as they did not have measurable disease at baseline by either criterion.

[‡]Based on RECIST v1.1 sum of longest diameter.

[§]Discontinued treatment due to progression.

"Other" includes glioneuronal, neuroepithelial, diffuse leptomeningeal, neuroblastoma, and recurrent small round blue cell brain tumors.

CR, complete response; HGG, high-grade glioma; LGG, low-grade glioma; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Fig. 2 Case study: Pediatric primary spinal high-grade glioma harboring an *ETV6-NTRK3* gene fusion (A) At baseline prior to commencing treatment with larotrectinib, and (B) After cycle 22 with no evidence of disease

A pediatric patient was diagnosed with primary spinal high-grade glioma at 4 months of age. The patient was treated with chemotherapy which consisted of 72 weeks of vincristine, cyclophosphamide, cisplatin and etoposide. The best overall response to this regimen was stable disease. At 3 years old, the patient experienced progression of disease. An *ETV6-NTRK3* gene fusion identified was identified and the patient was commenced on larotrectinib (**Figure 2A**). A complete response was achieved after two cycles of treatment and there was no evidence of disease after 22 cycles (**Figure 2B**). No significant adverse events were reported. Duration of treatment at the time of data cut-off was 15.7 months, with treatment ongoing.

NTRK, neurotrophic tyrosine receptor kinase.

Table 1. Patient characteristics

Characteristic	***n* = 33**
Sex, *n* (%)	
Male	17 (52)
Female	16 (48)
Age	
Median (range), years	8.9 (1.3–79.0)
Distribution, years, *n* (%)	
1 to <2	1 (3)
2 to <6	9 (27)
6 to <12	9 (27)
12 to <16	6 (18)
16 to <18	1 (3)
18 to <45	3 (9)
45 to <65	2 (6)
65 to <75	1 (3)
≥75	1 (3)
Prior cancer treatments, *n* (%)[a]	
Surgery	22 (67)
Radiotherapy	18 (55)
Systemic therapy	28 (85)
No. of prior systemic regimens, *n* (%)	
0	6 (18)[b]
1	12 (36)
2	8 (24)
≥3	7 (21)
***NTRK* gene fusion, *n* (%)**	
NTRK1	5 (15)
NTRK2	24 (73)
NTRK3	4 (12)

[a]Patients may be counted in more than 1 row.

[b]One patient who reported "Yes" to prior systemic therapies had the number of prior systemic therapies reported as zero.

NTRK, neurotrophic tyrosine receptor kinase.

Table 2. Efficacy

Parameter	*n* = 33
Response	
Evaluable patients	*n* = 33
Objective response rate, % (95% CI)	30 (16–49)
Pediatric patients (<18 years; *n* = 26)	38 (20–59)
Pediatric high-grade glioma (*n* = 13)	38 (14–68)
Pediatric low-grade glioma (*n* = 7)	43 (10–82)
Best response, *n* (%)	
Complete response	3 (9)[a]
Partial response	7 (21)[b]
Stable disease ≥24 weeks	15 (45)
Stable disease <24 weeks	5 (15)
Progressive disease	3 (9)
Disease control rate ≥24 weeks, *n* (%; 95% CI)[c]	24 (73; 54–87)
Pediatric patients (aged <18 years)	20 (77; 56–91)
Adult patients (aged ≥18 years)	4 (57; 18–90)
Duration of response	
Median, months (95% CI)	Not reached (3.8–NE)[d]
Range, months	3.8 to 22.0+
Ongoing response rate at 12 months,[e] % (95% CI)	75 (45–100)
Progression-free survival	
Median, months (95% CI)	18.3 (6.7–NE)[f]
Progression-free survival rate at 12 months,[e] % (95% CI)	56 (38–74)
Progression-free survival rate at 24 months,[e] % (95% CI)	42 (18–65)

Overall survival	
Median, months (95% CI)	Not reached (16.9–NE)[f]
Overall survival rate at 12 months,[e] % (95% CI)	85 (71–99)
Overall survival rate at 24 months,[e] % (95% CI)	58 (28–88)

[a]All complete responses were seen in pediatric cases: 2 in pediatric high-grade gliomas and 1 in pediatric non-glioma.

[b]All partial responses were seen in pediatric cases: 3 in pediatric high-grade gliomas with 2 pending confirmation, 3 in pediatric low-grade gliomas, and 1 in pediatric non-glioma.

[c]Disease control rate is the proportion of patients with best overall response of confirmed complete response, partial response, or stable disease lasting 24 weeks or more following the initiation of larotrectinib. Stable disease is measured from the date of the first dose of larotrectinib. Disease control rate calculation included 1 patient with unconfirmed partial response.

[d]In patients with confirmed responses (n = 8), with a median follow-up of 12.0 months.

[e]Kaplan–Meier estimates.

[f]In 33 patients with a median follow-up of 16.5 months.

CI, confidence interval; NE, not estimable.

Table 3. Treatment-emergent adverse events (*n* = 33)

	Overall treatment-emergent AEs, %[a]				Overall treatment-related AEs, %[b]		
Preferred term	Grade 1 or 2	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade
Upper respiratory tract infection	24	0	0	24	-	-	-
Vomiting	21	3	0	24	0	0	6
Diarrhea	21	0	0	21	0	0	3
Headache	18	3	0	21	0	0	3
Pyrexia	18	3	0	21	-	-	-
ALT increase	18	0	0	18	0	0	18
Anemia	18	0	0	18	0	0	18
Cough	18	0	0	18	0	0	3
AST increase	15	0	0	15	0	0	12
Constipation	15	0	0	15	-	-	-
Fatigue	15	0	0	15	0	0	6
Oropharyngeal pain	15	0	0	15	-	-	-
Viral infection	15	0	0	15	-	-	-
Conjunctivitis	12	0	0	12	-	-	-
Dysphagia	6	6	0	12	-	-	-
Ear pain	12	0	0	12	-	-	-
Nasopharyngitis	12	0	0	12	-	-	-
Neutrophil count decrease	9	3	0	12	3	0	12
Pneumonia	6	6	0	12	-	-	-
Urinary tract infection	9	3	0	12	0	0	3

	Neurological AEs of special interest, %[c]				**Treatment-related neurological AEs of special interest, %[b]**		
	Grade 1 or 2	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade
Headache	18	3	0	21	0	0	3

Ataxia	3	3	0	6	-	-	-
Balance disorder	3	3	0	6	-	-	-
Depressed level of consciousness	3	3	0	6	-	-	-
Dizziness	6	0	0	6	0	0	3
Facial paralysis	6	0	0	6	-	-	-
Hallucination	6	0	0	6	0	0	3
Hemiparesis	6	0	0	6	-	-	-
Hydrocephalus	3	3	0	6	-	-	-
Irritability	6	0	0	6	0	0	3
Memory impairment	6	0	0	6	0	0	6
Somnolence	6	0	0	6	-	-	-
Tremor	3	3	0	6	-	-	-

[a]The overall AEs listed here are those that occurred at any grade in ≥10% of patients, or at Grade 3 or 4 in ≥5% of patients regardless of attribution.

[b]Dashes indicate AEs that were not reported to be treatment-related in any patients.

[c]The neurological AEs of special interest listed here are those that occurred at any grade in ≥5% of patients.

Patients with multiple severity ratings for a given AE are counted once under the maximum severity.

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.

Figure 1

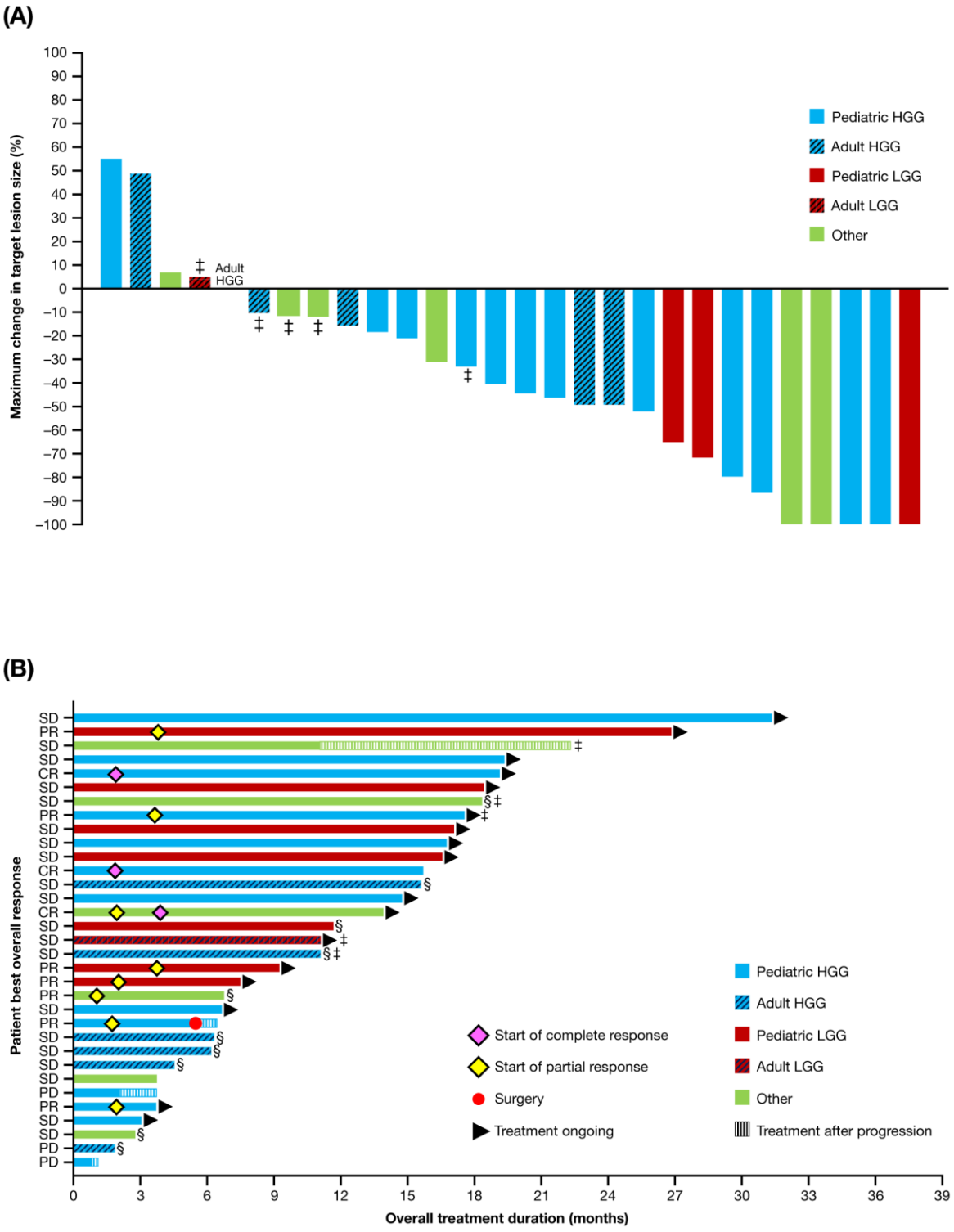

Figure 2